

Psychopharmacology for the Clinician Psychopharmacologie pratique

To submit questions for this regular feature, please send them to Journal of Psychiatry and Neuroscience/Revue de psychiatrie et de neuroscience, Royal Ottawa Hospital, LG 2044, 1145 ave. Carling Ave., Ottawa ON K1Z 7K4, Canada; fax 613 722-5871. Please include details of any relevant case and your name, address, telephone and fax numbers as well as your email address.

Question: How does grapefruit juice affect psychotropic medications?

A 75-year-old woman who had a 30-year history of depression had been in remission for 15 years while on fluoxetine. She had a relapse a year ago and did not respond to a dose increase. A trial of nefazodone made her too agitated. She eventually responded to fluvoxamine. After an episode of palpitations at a dosage of 200 mg every night, she achieved full remission of her depression at a dose of 150 mg every night. She was taking no other medications. One month later, in Florida for a vacation, she had palpitations, which stopped when she returned home. The only change identified was that while in Florida she drank grapefruit juice daily.

Answer

Fluvoxamine disposition is not as well defined as that of the other selective serotonin uptake inhibitors. It is affected to varying degrees by factors interacting with P450 2D6 and 2C19, and it can inhibit some of its own metabolism. P450 2D6 is responsible for the metabolism of numerous psychotropic medications. It is lacking in 5% to 10% of Caucasian and 1% to 2% of Asian people. As well,

about 8% of Caucasian people have duplicate genes that encode 2D6; these so-called "extensive metabolizers" may require higher doses due to their rapid metabolism.

There are numerous chemicals in grapefruit juice that act as inhibitors of P450 action. The flavonoid naringin and perhaps more so the furanocoumarin 6',7'-dihydroxybergamottin have both been shown to inactivate P450. These effects are selective to small-bowel wall epithelial P450 3A4 with little effect on hepatic P450 3A4. As with P450 inhibitors, the onset is rapid. Inhibition of P450 is fully developed after 1 glass of juice and lasts up to 24 hours. Other studies have also found that 6',7'-dihydroxybergamottin inhibits the actions of P450 1A2, 2A6, 2C9, 2C19, 2D6, and 2E1, but to a lesser extent than for 3A4.

Nefazodone and trazodone both have the highly anxiogenic metabolite meta-chlorophenylpiperazine, which is normally metabolized by 2D6. Patients deficient in 2D6 will have marked anxiety when given either of these medications. They will also not respond to codeine, which requires 2D6 metabolism to morphine to be effective. These clues can be used to guide treatment choices so as to avoid or take extra precautions when prescribing

medications that are metabolized by P450 2D6.


Putting this information together, we can conclude that the patient in this case is likely deficient in 2D6, which explains her agitation with nefazodone. Fluoxetine is a minor substrate for 2D6, so that the deficiency probably was not sufficient to cause problems while she was on this antidepressant. Nevertheless, it might have been sufficient so that in the presence of grapefruit juice, the lesser inhibition of 2D6 alone or together with inhibition of 2C19 was enough to raise fluvoxamine levels, which in turn could further inhibit its own metabolism. One result of increased fluvoxamine could be the palpitations (a problem in about 5% of patients on this medication) that she had when previously on the 200 mg dose.

Grapefruit juice is one of the more potent P450 inhibitors and should be considered and discussed when prescribing any medication metabolized by the P450 system.

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The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.

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